A STUDY OF RHEUMATOID FACTOR AND ITS RELATION TO ISCHEMIC HEART DISEASE

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CERTIFICATE

This is to certify that this dissertation entitled **"A STUDY OF RHEUMATOID FACTOR AND ITS RELATION TO ISCHEMIC HEART DISEASE"** submitted by **Dr.P.JAYAPANDIAN** appearing for Part II M.D. Branch I General Medicine Degree examination in March 2009 is a bonafide record of work done by him under my direct guidance and supervision in partial fulfillment of regulations of The Tamil Nadu Dr. M.G.R. Medical University, Chennai. I forward this to The Tamil Nadu Dr.M.G.R. Medical University, Chennai, Tamil Nadu, India.

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I solemnly declare that the dissertation entitled **"A STUDY OF RHEUMATOID FACTOR AND ITS RELATION TO ISCHEMIC HEART DISEASE**" is done by me at madras medical college, Government General Hospital, Chennai during 2006-2008 under the guidance and supervision of **Prof .D. RAJASEKARAN, M.D.** This dissertation is submitted to The Tamilnadu Dr. M.G.R Medical University, towards partial fulfillment of regulation for the award of **M.D. DEGREE IN GENERAL MEDICINE (BRANCH–I).**

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CONTENTS

INTRODUCTION

Ischemic heart disease (IHD) is a leading cause of death in the western world and increased incidence in our country also. Most of the subjects with IHD have one or more traditional risk factors including diabetes, smoking history, hypertension, obesity, a family history of IHD and hyperlipidimia. In recent years new risk factors for IHD have been identified, including the presence of inflammation as demonstrated by raised highly sensitive C-reactive arthritis(RA),Antiphospholipid antibody syndrome and systemic lupus erthematosus also have a greatly increased risk of developing IHD.

The autoantibody rheumatoid factor (RF) is strongly associated with RA, may be present in subjects many years before they develop RA and its presence confers a risk of developing RA that increases with increasing titre. However RF is associated with other autoimmune rheumatic disease, viral or bacterial infections and is present in as many as 15% of normal adults. Recently, RF has been associated with an increased likelihood of developing IHD in patients with inflammatory polyarthrities.

Presence of RF in general population may identify the subjects with a similar immune pathology to patients with RA ,who may also share an increased

likelihood of developing IHD and that RF may have special role in the pathogenisis of IHD.

To explore this, the study was conducted whether the presence of RF was associated with increased risk of IHD among general population.

AIMS AND OBJECTIVES

1. To analyse the RF is an indipendent and additional risk factor for IHD in general population.
2. And comparing in male/female ,and correlation between high titre and low titre of RF in the effect of IHD with or without traditional risk factor.

REVIEW OF LITERATURE

The coronary circulation is unique in that it iresponsible for generating the arterial pressure that is required to perfuse the systemic circulation and yet at the same time has its own perfusion impeded during the systolic portion of the cardiac cycle. Because myocardial contraction is closely connected to coronary flow and oxygen delivery, the balance between oxygen supply and demand is a critical determinant of the normal beat to beat function of the heart. When this relationship is acutely disturbed by disease affecting coronary blood flow, the resulting imbalance can immediately precipitate a vicious cycle, where by ischemia-induced contractile dysfunction precipitates hypotension and further myocardial ischemia. IHD causes more deaths and disability and incurs greater economic costs than any other illness in the developed world. IHD is the most common, serious, chronic, life-threatening illness in the world wide. A high fat and energy-rich diet, smoking, and a sedentary lifestyle are associated with the emergence of IHD. In the United States and Western Europe, it is growing among low-income groups rather than high-income groups (who are adopting more healthful lifestyles), while primary prevention has delayed the disease to later in life in all socioeconomic groups.

Obesity, insulin resistance, and type 2 diabetes mellitus are increasing and are powerful risk factors for IHD. With urbanization in the developing world, the prevalence of risk factors for IHD is increasing rapidly in these regions such that a majority of the global burden of IHD is now occurring in low-income and middle-income countries. Population subgroups that appear to be particularly affected are men in South Asian countries, especially India. Given the projection of large increases in IHD throughout the world, IHD is likely to become the most common cause of death worldwide by 2020

Central to an understanding of the pathophysiology of myocardial ischemia is the concept of myocardial supply and demand. Under normal conditions, for any given level of a demand for oxygen, the myocardium will be supplied with oxygen-rich blood to prevent underperfusion of myocytes and the subsequent development of ischemia and infarction.

The major determinants of myocardial oxygen demand are heart rate, myocardial contractility, and myocardial wall tension (stress). An adequate supply of oxygen to the myocardium requires a satisfactory level of oxygen-carrying capacity of the blood (determined by the inspired level of oxygen, pulmonary function, and hemoglobin concentration and function) and an adequate level of coronary blood flow. Blood flows through the coronary arteries in a phasic

fashion, with the majority occurring during diastole. About 75% of the total coronary resistance to flow occurs across three sets of arteries:

(1) large epicardial arteries

(2) prearteriolar vessels

(3) arteriolar and intramyocardial capillary vessels.

In the absence of significant flow-limiting atherosclerotic Obstruction, the normal coronary circulation is dominated and controlled by the heart's requirements of oxygen. This need is met by the ability of the coronary vascular bed to vary its resistance (and, therefore, blood flow) considerably while the myocardium extracts a high and relatively fixed percentage of oxygen. Normally, intramyocardial resistance vessels demonstrate an immense capacity for dilation. For example, the changing oxygen needs of the heart with exercise and emotional stress affect coronary vascular resistance and in this manner regulate the supply of oxygen and substrate to the myocardium (*metabolic regulation*). The coronary resistance vessels also adapt to physiologic alterations in blood pressure in order to maintain coronary blood flow at levels appropriate to myocardial needs (*autoregulation*).

By reducing the lumen of the coronary arteries, atherosclerosis limits appropriate increases in perfusion when the demand for flow is augmented, as occurs during exertion or excitement. When the luminal reduction is severe, myocardial perfusion in the basal state is reduced. Coronary blood flow can also be limited by spasm, arterial thrombi, and, rarely, coronary emboli as well as by ostial narrowing due to aortitis. Congenital abnormalities,such as origin of the left anterior descending coronary artery from the pulmonary artery, may cause myocardial ischemia and infarction in infancy, but this cause is very rare in adults.

Myocardial ischemia can also occur if myocardial oxygen demands are markedly increased and when coronary blood flow may be limited, as occurs in severe left ventricular hypertrophy due to aortic stenosis. The latter can present with angina that is indistinguishable from that caused by coronary atherosclerosis largely owing to subendocardial ischemia.A reduction in the oxygen-carrying capacity of the blood, as in extremely severe anemia or in the presence of carboxyhemoglobin, rarely causes myocardial ischemia by itself but may lower the threshold for ischemia in patients with moderate coronary obstruction.

Not infrequently, two or more causes of ischemia coexist, such as an increase in oxygen demand due to LV hypertrophy secondary to hypertension and a reduction in oxygen supply secondary to coronary atherosclerosis and anemia. Abnormal constriction or failure of normal dilation of the coronary resistance

vessels can also cause ischemia. When it causes angina, this condition is referred to as *microvascular angina.*

From a practical viewpoint, the cardiovascular risk factors that have emerged from such studies fall into two categories: those modifiable by lifestyle and/or pharmacotherapy and those that are essentially unmodifiable. The weight of evidence supporting various risk factors differs. For example, hypercholesterolemia and hypertension certainly predict coronary risk, but other so-called nontraditional risk factors, such as levels of homocysteine, lipoprotein (a) , or infection, remain controversial. One must further distinguish factors that actually participate in atherogenesis from those that may merely serve as markers of risk without direct involvement in pathogenesis. The following Lists the risk factors recognized by the current National Cholesterol Education Project Adult Treatment Panel- III. The sections below will consider some of these risk factors and approaches to their modification.

- Cigarette smoking
- Hypertension (BP $\geq$ 140/90 mmHg or on antihypertensive medication)
- Low HDL cholesterol[<1.0 mmol/L (<40 mg/dL)]
- Diabetes mellitus

- Family history of premature CHD
    - CHD in male first-degree relative <55 years
    - CHD in female first-degree relative <65 years
- Age (men ≥45 years; women ≥55 years
- Lifestyle risk factors
    - Obesity
    - Physical inactivity
    - Atherogenic diet
- Emerging risk factors
    - Lipoprotein(a)
    - Homocysteine
    - Prothrombotic factors
    - ***Proinflammatory factors***
    - Impaired fasting glucose
    - Subclinical atherogenesis

Ischemic heart disease is most often due to atherosclerotic coronary artery disease. The importance of inflammation in atherosclerosis is also supported by the finding of inflammatory cells in atherosclerotic lesions . The following conditions are associated with inflammatory/ proinlammatory factors causative factors for IHD.

1) Rheumatoid arthritis

2) Systemic lupus erthymatosus

3) Antiphospholipid antibody syndrome

4) Vassculitis producing other connective tissue disorders

Of these inflammatory/ proinflammatory factor, RF is one of the independent and additional risk factor for IHD.

ROLE OF RHEUMATOID FACTOR IN IHD

The association of RF with IHD provides further of an importance of inflammation and raises the possibility that autoimmune mechanisms may playing a part. The study cannot determine whether RF is a non-specific marker of inflammation or is involved directly in pathogenesis of atherosclerosis in the subjects included. However , RF appears to cause direct tissue damage in RA as a constituent of immune complexes, perhaps by activating complement. It might cause damage to the vascular endothelium in the same way.

There is circumstancial evidence for this: Atherosclerotic plaques contain immunoglobulins and complements suggesting immune complex activity. In addition the lack of relationship between IHD and the autoantibodies ANA and ACA suggests that the association between RF and IHD.This may not be due to non-specific polyclonal B-cell activation secondary to inflammation but the unique role of RF in the pathogenesis of atherosclerosis/IHD.

This is further supported by the association of RF with IHD in subjects with inflammatory arthritis. There is also an intriguing possibility that the the pathological process involved in IHD such as atheroma formation, may generate inflammatory tissue capable of producing RF. Infections cause inflammation and can induce RF production, although this is usually short lived. Chronic infections that induce persistent RF is rare. Acute infections are associated with an increased risk of cardiovascular events, perhaps by inducing circulating cytokines or an autoimmune response.

RHEUMATOID ARTHRITIS (RA)

Patients with rheumatoid arthritis have an increased prevalence of IHD. This is most likely in those people with the autoantibody RF.Which are strongly associated with RA but is also present in up to 15% of all adults. Atherosclerotic plaque is a complex inflammatory lesion characterized by an infiltrate of macrophages and T cells. Intra plaque immune cells are activated and involved in mediating tissue injury. T-cell cytokines can drive macrophage activation in atherosclerotic lesions and can also regulate the acute-phase response. Indeed, T cells in patients with acute coronary syndromes (ACS) are skewedtoward the production of interferon (IFN)-γ, a potent monoyte activator largely derived from a distinct subset of CD4+ T cells that, in contrast to classic CD4+ helper T cells, lacks the co-stimulatory molecule CD28. CD4+CD28null T

cells are clonally expanded in ACS and invade the unstable atherosclerotic plaque.

Moreover, CD4+CD28null T cells have cytotoxic capability, can effectively kill Endothelial cells *in vitro*, and may contribute to endothelial cell injury in coronary plaque. Expansion of CD4+CD28null T cells was initially described in patients with rheumatoid arthritis (RA), a chronic autoimmune disease of unknown etiology. RA is characterized by chronic inflammation and hyperplasia of synovial tissue. More importantly, it is a quintessential systemic disease that can manifest in most major organ systems.

T cells play a central role in the Immune pathogenesis of RA and are the key regulators of the chronic destructive joint lesions. In addition, patients with RA have abnormalities in T-cell homeostasis that affect the entire pool of T cells. One of the consequences of dysregulated T-cell homeostasis is the emergence of large clonal CD4+CD28 null T-cell populations that are auto reactive and cytotoxic, and infiltrate synovial tissue. The highest frequency of CD4+CD28null T cells is found in severe RA, particularly in patients with rheumatoid vasculitis.

When the inflammatory process in RA spreads to extra-articular sites, such as mid-size arteries and capillaries, morbidity and mortality are clearly increased. The inflammatory mechanisms in RA may enhance atherogenesis in several ways. C-reactive protein, a useful marker of disease activity, is elevated in

RA and has prognostic value. It may also participate directly in endothelial injury by sensitizing endothelial cells to T-cell mediated cytotoxicity.

Circulating cytokines in RA, such as TNF-α, result in endothelial activation and up-regulation of adhesion molecules. Indeed, endothelial dysfunction is frequently present in RA patients, even in the absence of identifiable Cardiovascular risk factors and improves with anti-TNF-α therapy . Cytokines will also non-specifically activate monocytes and other cells of the innate immune system. RA is characterized by the expansion of auto reactive T-cell clones that typically lack CD28. The frequency of such CD4+CD28 null T cells correlates with disease severity with respect to erosive progression and extra-articular manifestations. The frequency in the RA with CAD cohort (median 3.5%) was higher than in historical controls of patients with RA and absence of extra-articular manifestations, suggesting that CV co-morbidity in RA is correlated with disease severity and that CD4+CD28null T cells may be involved in the Cardio Vascular complications of RA. CD4+CD28nullT cells have been directly implicated in the pathogenesis of coronary artery disease. Persistent activation of such auto reactive cells in RA may result in a vicious cycle of cytokine release, mononuclear cell activation and tissue injury.

However, we cannot exclude the possibility that the high CD4+CD28null T cells levels in RA with CAD patients is reflective of an increased RA disease

severity in these patients. Addressing this issue further will require comparing RA patients that are matched for disease severity.

The impact of severe RA on mortality may be mediated via reduced physical activity that will compromise cardio respiratory fitness. This might contribute to higher Cardio vascular mortality in RF-positive RA patients. Disability has been shown to be a predictor of all-cause and Cardiovascular mortality in early inflammatory polyarthritis and established RA.

More severe RA is also associated with a higher cumulative inflammatory disease burden. Atherosclerosis is now accepted to be an inflammatory condition, and elevation of inflammatory markers including high-sensitivity C-reactive protein (CRP) has been associated with the subsequent development of Cardio vascular events in the general population, and histological study has identified the presence of inflammatory cells in atherosclerotic plaque in the general population. If atherosclerosis is promoted by chronic low-grade inflammation, as suggested by Ridker, it is plausible that atherosclerosis may be accelerated in chronic systemic inflammatory conditions like RA. A previous study of the Rochester RA cohort demonstrated that cumulative inflammation measured using the erythrocyte sedimentation rate (ESR) was associated with subsequent Cardio vascular events. In addition, modest elevations in baseline CRP were associated with subsequent

Cardio vascular mortality in patients with early inflammatory polyarthritis who were registered with the Norfolk Arthritis Register.

Effective drug therapy, which reduces inflammation in RA, has been shown to reduce all-cause and CVD mortality, and responders to anti-tumor necrosis factor-a therapies were found to have a lower incidence of myocardial infarction than non-responders. Therefore RF-positive patients may have increased ischemic heart disease mortality because they have increased levels of chronic inflammation, and suppression of this inflammation may lead to improved survival.

Other factors associated with RF status and severity of RA include anti-CCP status and presence of the HLA-DRB1 shared epitope. High titers of anti-CCP predicted mortality in a study of RA patients in Finland. A recent study reported that, while RF status and anti-CCP status were each associated with mortality in inflammatory polyarthritis, possession of both markers did not confer a higher mortality risk. In addition there was a significant interaction between these 3 variables in the models predicting mortality. Therefore mortality outcome in inflammatory arthritis appears to be associated with variables that promote more severe disease.

It has been hypothesized that circulating immune complexes and RF might have a direct effect on endothelial cells to promote atherosclerosis. Dessein, *et al*

reported that RF and interleukin 6 were associated with biomarkers of endothelial dysfunction in RA patients, even after adjusting for traditional CVD risk factors. Impaired nitrate-mediated vascular dilation was found to be associated with circulating levels of immune complexes in RA, and this has been suggested to be one of the mechanisms by which atherosclerosis is promoted in RA. It is interesting to note that B lymphocytes have been identified in atherosclerotic plaques of RA patients[51], while in atherosclerotic plaques of non-rheumatoid patients T lymphocyte infiltration is observed. Therefore there is some modest evidence that RF may be involved in the pathogenesis of atherosclerosis in RA.

Excess mortality in RA is largely confined to those who are RF-positive. It is still unclear whether RF itself contributes to the reduced life expectancy of patients with RA, or whether it is simply a marker for more severe disease and higher cigarette smoking exposure. Early use of disease modifying antirheumatic drugs and use of biologic agents to suppress inflammatory disease is likely to influence the life expectancy of these patients, and it will be interesting to explore whether cardio vascular disease outcomes in patients treated with B cell suppression are improved. However, it is likely that a combined approach is required, with modification of lifestyle factors, as well as suppression of the inflammatory disease process, to improve the mortality outcome in RF-positive subjects.

RA is characterized by chronic inflammation and hyperplasia of synovial tissue. More importantly, it is a quintessential systemic disease that can manifest in most major organ systems. T cells play a central role in the immunopathogenesis of RA and are the key regulators of the chronic destructive joint lesions. In addition, patients with RA have abnormalities in T-cell homeostasis that affect the entire pool of T cells. One of the consequences of dysregulated T-cell homeostasis is the emergence of large clonal $CD4^{+}CD28^{null}$ T-cell populations that are auto reactive and cytotoxic, and infiltrate synovial tissue. The highest frequency of $CD4^{+}CD28^{null}$ T cells is found in severe RA, particularly in patients with rheumatoid vasculitis. When the inflammatory process in RA spreads to extra-articular sites, such as mid-size arteries and capillaries, morbidity and mortality are clearly increased.

Because the chronic inflammatory process and immune dysregulation in RA have features in common with those involved in atherosclerosis, they could predispose patients with RA to accelerated CAD. Several studies have documented an increased risk of atherosclerosis and myocardial infarction in patients with RA. In addition, RA is associated with a reduced life expectancy, primarily because of excessive deaths from cardio vascular disease. RA is a heterogeneous disease, and the disease phenotype itself is predictive of mortality; patients with more severe clinical disease have higher mortality rates. Overall mortality is also increased in

patients who are positive for the autoantibodies, rheumatoid factors. In addition, the extent of inflammation in RA has been linked to an increased risk of cardio vascular mortality. The number of swollen joints, independent of traditional cardio vascular risk factors, is predictive of cardio vascular related deaths among Pima Indians with RA. The strongest association with increased cardio vascular mortality is seen in patients with extra-articular manifestations of RA.

Inflammation is part of the process of atherosclerotic disease, and patients with inflammatory diseases, such as rheumatoid arthritis and systemic lupus erthymatosus, are at increased risk for cardiovascular events. Among patients with rheumatoid arthritis, testing positive for circulating rheumatoid factor (RF) represents an added risk for ischemic heart disease.RF may be present in 15% of the general population without clinical rheumatoid arthritis. This factor may be acquired through the presence of other autoimmune disease or previous bacterial infections. In addition, it appears that smokers have higher rates of testing positive for RF. The current study examines whether RF represents an independent risk factor for ischemic heart disease in a general population of patients.

In the general population, the presence of advanced atherosclerosis on angiography is predictive of a worse prognosis. The extent of atherosclerosis determined by angiography has not been studied in RA. Indirect evidence of accelerated atherosclerosis in RA comes from studies using carotid artery intima

medial thickness as a marker of atherosclerotic burden and vascular risk. Increased intima-media thickness was independent of traditional Cardio vascular risk factors but was related to RA disease activity, duration and severity.Data presented here suggest that the acceleration of atherosclerotic disease in RA holds for multiple vascular beds, lending support to a systemic disease mechanism.

Patients with RA have a significantly higher prevalence of angina pectoris. Also, women with RA have a significantly increased risk of myocardial infarction compared with those without RA. This excess of Cardio vascular disease in RA cannot be explained by the traditional Framingham risk factors and probably arises from the underlying disease and/or its treatment. There is no evidence that disease-modifying antirheumatic drug (DMARD) therapy increases mortality in RA. Corticosteroids can cause dyslipidemia, hyperglycemia and hypertension but may also control inflammation in RA. Studies have attempted to define the impact of steroids on mortality in RA but the results are inconsistent.DMARD treatment can actually improve the outcome in RA. Choi and colleagues have demonstrated that methotrexate-treated patients had a 70% reduction in CV deaths compared with those who did not receive disease-modifying therapy. Other DMARDs such as sulfasalazine, penicillamine, hydroxychloroquine, and gold did not confer this protection. Thus, the RA disease process itself likely contributes to accelerated CAD.

The inflammatory mechanisms in RA may enhance atherogenesis in several ways. C-reactive protein, a useful marker of disease activity, is elevated in RA and has prognostic value. It may also participate directly in endothelial injury by sensitizing endothelial cells to T-cell mediated cytotoxicity. Circulating cytokines in RA, such as TNF-α, result in endothelial activation and up-regulation of adhesion molecules. Indeed, endothelial dysfunction is frequently present in RA patients, even in the absence of identifiable CV risk factors and improves with anti-TNF-α therapy. Cytokines will also non-specifically activate monocytes and other cells of the innate immune system. RA is characterized by the expansion of auto reactive T-cell clones that typically lack CD28. The frequency of such $CD4^{+}CD28^{null}$ T cells correlates with disease severity with respect to erosive progression and extra-articular manifestations. The frequency in the RA with CAD cohort (median 3.5%) was higher than in historical controls of patients with RA and absence of extra-articular manifestations, suggesting that CV co-morbidity in RA is correlated with disease severity and that $CD4^{+}CD28^{null}$ T cells may be involved in the CV complications of RA.$CD4^{+}CD28^{null}$ T cells have been directly implicated in the pathogenesis of coronary artery disease. Persistent activation of such autoreactive cells in RA may result in a vicious cycle of cytokine release, mononuclear cell activation and tissue injury.However, we cannot exclude the possibility that the high $CD4^{+}CD28^{null}$ T cells levels in RA with CAD patients is

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SYSTEMIC LUPUS ERTHTYMATOSUS

Atherosclerotic disease is common in systemic lupus erthymatosus and is the result of multiple pathogenic mechanisms that include traditional risk factors as well as SLE-related factors. Endothelial dysfunction and arterial stiffness contribute significantly to the Atherogenic process Accelerated atherosclerosis is a significant cause of morbidity and mortality in systemic lupus erthymatosus. Both arteritis and atherosclerosis can involve the coronary arteries of young patients suffering from SLE. Coronary arteritis, though rare, occurs in association with active vasculitis in other organs such as skin, spleen, kidneys, etc. Coronary spasm in SLE patients is rare, and when it occurs, it is usually in relation to the two common pathological processes mentioned above.

Systemic lupus erthymatosus is an autoimmune disorder affecting multiple organ systems. Patients with systemic lupus erthymatosus exhibit a bimodal pattern of mortality, with those who have had the disease for 5 to 10 years being at increased risk of cardiovascular disease,particularly myocardial infarction. Elevated levels of conventional cardiovascular risk factors promote vascular damage resulting in impairment of normal endothelial function. In addition, autoantibodies directed against oxidized lipoproteins, along with chronic secretion of inflammatory cytokines and suppression of fibrinolytic parameters, are thought to increase atherogenesis. It is no longer a matter of dispute that SLE patients have

an increased risk of developing atherosclerotic cardiovascular disease, particularly before the age of 50. The incidence of coronary heart disease in women with SLE aged 35–44 years has been estimated to be 50- fold greater than in the general population, and the cumulative prevalence of CAD in SLE patients was 8.9%. Early detection and management of atherosclerosis may reduce the morbidity and improve the survival of patients with SLE.

Coronary artery vasculitis remains an infrequent complication of SLE. Prior to the widespread use of coronary angiography, coronary vasculitis was a post mortem diagnosis. Coronary angiography has helped in evaluating patients with suspected coronary vasculitis. It has been suggested that a rapid rate of progression of coronary lesions is more suggestive of a vasculitic process and, therefore, single angiographic studies may be inadequate. One case report documented a tertiary referral center experience where only two patients younger than 35 years of age with coronary vasculitis were identified over a period of 40 years. A possible mechanism of arterial injury in SLE might be the development of auto-antibodies that may target the heart or the blood vessels. According to Dangas et al., there are increased auto-antibodies against actin and myosin during and after an acute coronary syndrome. The present case represents only the fourth case reported in detail with SLE and coronary artery disease in a patient younger than 21 years old. The diagnosis of coronary vasculitis secondary to SLE in this case is suggested by

the documentation of the diagnosis of SLE, the absence of classic risk factors for atherosclerotic heart disease (no evidence of diabetes, hypertension, family history of CAD or smoking) and the occurrence of angina pectoris or myocardial infarction at a young age.

In addition to premature coronary artery disease, there was clearly a rapid change in the patient's anatomy after coronary artery bypass graft surgery with total occlusion of 3 out of 4 grafts over only a 4-month period. The fourth graft displayed segmental narrowing. This is higher than early occlusion rates reported in multiple trials. Also, the internal mammary artery of our patient displayed areas of fibrosis and intimal thickening per the operative report,precluding its use as a graft. These events suggest vasculitis as a possible etiology for her deterioration, as is suggested from the pathology slide. Immune complex deposition in the coronary artery walls in patients with SLE have been documented via immunofluorescence studies and the relationship between inflammatory immunologic injury and atherosclerosis has been demonstrated experimentally. Similar immune complex deposition in coronary vessels of SLE patients may predispose to intimal thickening and atherosclerosis, thus increasing the frequency of myocardial infarction. Histologic findings at autopsy have displayed both neutrophilic and lymphocytic infiltration, fibrinoid necrosis and immune complex deposition.

The etiology of the accelerated atherosclerosis in SLE in not known, but it has been linked to inflammation and endothelial dysfunction, a consequence of the inflammatory process. Flow-mediated dilatation is a non-invasive method of measurement of endothelial dysfunction. It is based on the change in diameter of a conduit artery in response to increased flow, typically induced by a period of ischemia in the distal circulatory bed.

The formation of immune complexes in patients with SLE is strongly associated with acceleration of atherogenesis.The presence of autoantibodies to β2-glycoprotein-1 and HDL-associated protein and major antigen for anticardiolipin antibodies, is strongly associated with inflammation in patients with SLE as are autoantibodies to components of oxidized LDL. In patients with SLE, immune complexes activate complement, which in turn acts on mast cells and basophilsto release vasoactive amines. These amines, which include histamine and 5-hydroxytryptamine, promote endothelial cell retraction and increased vascular permeability, induce the expression of endothelial adhesion molecules, and attract polymorphs that subsequently infiltrate the area of damage Thrombin and inflammatory cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor–α are also involved in this process. Following the trigger of adhesion molecule expression, preformed P-selectin is rapidly but transiently translocated to the endothelial surface, and within hours E-selectin is also expressed .

Subsequently, integrin molecules on the leukocytes bind to immunoglobulin superfamily receptors. For example, β2-integrins bind to intercellular adhesion molecule–1, and monocyte α4β1 integrin binds to vascular cell adhesion molecule–1 (VCAM-1). These molecules promote the capture and rolling of the leukocytes. Pro-oxidant molecules stimulate endothelial nuclear factor κB (NF-κB), thereby promoting expression of VCAM-1 and monocyte chemotactic protein–1 (MCP-1), and subsequently monocyte infiltration, by interaction with platelet-endothelial cell adhesion molecule. In diabetic patients, advanced glycosylation endproducts also mediate prolonged expression of NF-κB, and may be a mechanism for the similar increased risk of cardiovascular complications.28 Nitric oxide induces the endogenous inhibitor of NF-κB, IκBα, which reduces expression of both VCAM-1 and MCP.

Advances in medical therapy and a better understanding of systemic lupus erythematosus (SLE) have contributed to a dramatic improvement in the long-term survival of patients. However, despite the overall long-term improvement, coronary artery disease remains a major cause of morbidity and mortality with an incidence that is approximately nine-fold greater than would be expected for this population. Following active lupus, coronary artery disease is the second most common cause of hospitalization for SLE patients. Manzi et al. found that, when controlled for age and gender, women with SLE who are 35–44 years old have a

50-times higher risk of myocardial infarction (MI). Previous autopsy studies have observed that severe coronary artery disease is present in as many as 40% of patients with SLE compared with only 2% of age-matched controls at the time of death.

Etiologies of myocardial damage in SLE patients include premature atherosclerotic disease, antiphospholipid antibody syndrome,8 coronary artery spasm, coronary artery vasculitis and restenosis after percutaneous revascularization procedures. The present case illustrates the importance and challenge of differentiating among these etiologies, especially since the therapies used are different in each situation. The following discussion ill focus on the diagnosis and pathogenesis of coronary artery disease with an emphasis on premature atherosclerosis and coronary vasculitis in patients with SLE.

ANTIPHOSPHOLIPIDS ANTIBODY SYNDROME

The antiphospholipid syndrome (APS) is an acquired thrombotic disorder characterized by recurrent venous or arterial thrombosis or recurrent miscarriages, or both, associated with the presence in the serum of IgG or IgM anticardiolipin antibodies (aCL) and/or lupus anticoagulant (LAC). APS may occur as a primary disorder (PAPS) or associated with connective tissue diseases, mainly systemic lupus erthymatosus (secondary APS).Primary and secondary APS are both associated with a significant increase of cardiovascular risk.

Atherosclerosis is an autoimmune/inflammatory disease associated with infectious, inflammatory, and autoimmune factors. Both humoral and cellular immune mechanisms have been proposed to participate in the onset and/or progression of atheromatous lesions. Heat-shock protein (hsp), oxidized low-density lipoprotein (LDL), and beta2-GPI have been reported to elicit humoral and cellular immune response in both experimental animals and humans.

Antiphospholipid (antibody) syndrome is a pathological condition that is also referred to as "Hughes syndrome." It originates from excess accumulation of blood clots by antiphospholipid antibodies. The syndrome may occur as a primary condition (primary APS) or along with the autoimmune disease, systemic lupus erthymatosus. SLE is a chronic disease that affects certain organs, blood vessels, or the skin. The main signs of APS include blotchy skin, migraine, memory loss, fatigue, deep vein thrombosis, pulmonary embolism, and stroke. Primary APS may affect heart valves and present with such damage in 30% of patients. In pregnant women with APS, miscarriages may occur. In this overview, we present an up-to-date description and synthesis of the main vascular ischemic (occlusive) diseases with neuropsychiatric symptomatics in APS. The recognition that a number of SLE manifestations have a thrombotic rather than an inflammatory basis can be considered one of the most important recent contributions to rheumatology and immunology. The "anticardiolipin syndrome" described by

Graham Hughes in the 1980s,1 which was subsequently renamed antiphospholipid (Hughes) syndrome, appeared as a frequent condition in patients with SLE2 but also was present in others without SLE or other autoimmune diseases. In such cases it was termed a "primary" APS (PAPS). Almost 20 years after its definition, APS has crossed over into many fields of medicine. However, the full spectrum of the syndrome has yet to be defined, and significant advances in the diagnosis and management of patients with APS have been made. In addition, a consensus about very important questions, such as the use of alternative tests for anticardiolipin (aCL) antibodies and lupus anticoagulant (LA) assays, the treatment of pregnancy failure, or the intensity of anticoagulant therapy, has not yet been achieved.

These autoantigens are expressed within atherosclerotic lesions. Immunization with the given autoantigens elicits an immune response that influences lesion progression. Atherosclerosis susceptibility can be transferred by autoantigen-sensitized lymphocytes from immunized animals. Patients with systemic lupus erthymatosus (SLE) and antiphospholipid syndrome (APS) have a high risk for atherosclerotic cardiovascular events. The traditional risk factors fail to fully account for accelerated atherosclerosis in SLE and APS. Immunological alterations, such as antibodies to oxidized LDL, antiphospholipid antibodies (aPL), antibodies to beta-2 Glycoprotein (anti-beta2-GPL), anti-prothrombin antibodies, may play a role in premature atherosclerosis in SLE and APS. aPLs predict an

increased risk for MI, and their levels are increased in young survivors of MI. ß2GP1 is a cofactor for antibody binding to cardiolipin,and recent studies indicate that many aCLs recognize oxidized CL (OxCL) and/or adducts of OxCL with ß2GP1. The antiphospholipid antibody syndrome is characterized by both arterial and venous thrombosis and is common in SLE. In the present study, lupus anticoagulant showed a significant association with IHD in SLE. In addition, both aCLs and anti-ß2GPI antibodies tended to be associated with arterial disease in SLE. It is possible, therefore, that the increased risk of IHD in SLE is to some extent caused.

It is assumed that aPL are a significant risk factor for AMI in selected patients. According to Adler et al, aPL precede the infarction, rather than follow it. The results we obtained regarding the frequency of APS in AMI (38%) are a little higher, as compared with authors cited above. This could be attributable to proper initial selection of patients, suspected for APS. The increased values of ACA, ß2GP1 antibodies and CD31 registered in patients with AMI correlate well with the development of arterial thrombosis, and some disputable pathogenic mechanisms of arising of hyper coagulation in patients with APS. According to Galli et al, the presence of ACA and ß2GP1 antibodies in patients with systemic lupus erthymatosus is connected with a risk for development of arterial thrombosis. Many authors consider ß2GP1, which is the main co-factor of binding between

ACA and cardiolipin, as one of the key structures. On the other hand, a direct formation of antibodies against ß2GP1 is also observed in APS. The importance of ß2GP1 is connected with its functions of a natural coagulant, namely the blocking of the contact system of coagulation , inhibition of adenosin diphosphate-depending aggregation and the synthesis of factor Xa from the activating platelets, as well as the inhibition of prothrombinase activity of inactivated platelets . Recently, there are reports that in patients with secondary APS, antibodies against ß2GP1 can be used as a target for immune mediated atherogenesis. Anti- ß2GP1 antibodies can trigger other mechanisms - to activate the endothelium cells and activate adhesion molecules such as ICAM-1, VCAM-1, and E-selectine.

The arising of thrombosis in APS is also associated with increased activity of thrombotic endothelium adhesion molecules CD31. CD31 is expressed on platelets, neutrophils, monocytes and endothelium cells, and it plays a significant role in their interaction. Apart from the signal function it has,CD31 also activates the ß-3 subgroup of integrins, which in turn play a crucial role in the adhesion of cells. It is not by chance that the flowcytometric investigation of the expression of CD31 on the circulating platelets is recommended as an important method for investigating thrombotic conditions. The results we obtained of increased expression of the marker in the chronic stage of myocardial infarction correlate

well with the observation in cases of following thrombosis, and they prove the significance of CD31 in the pathogenesis of APS.

In conclusion, we consider that the investigations we carried out confirm the proposition that aPL play an important role in the pathogenesis of acute coronary incidences. The timely diagnosis of APS could improve the prognosis, prevention and treatment of patients in this risk group.

MATERIALS

SUBJECTS:

Patients who are all positive to Rheumatoid factor attending Govt. General Hospital between May 2006—may2008

PERIOD OF STUDY:

May2006—may 2008

DESIGN OF STUDY

Cross sectional observational study

ELIGIBILITY CRITERIA

All patients with RF positive by ELISA

INCLUSION CRITERIA

1. Hypertension
2. Obesity
3. Diabetes mellitus
4. H/O smoking,
5. H/o IHD
6. Family h/o IHD

EXCLUSION CRITERIA

1. Chronic infection
2. Elderly patients (>60 years)
3. Patients with thyroid abnormality

METHODOLOGY

One hundred patients with rheumatoid arthritis and who were positive for RF attending Govt.General Hospital during the study period evaluated for IHD by ECG and ECHO.

Those who are included in the study were evaluated for traditional risk factors h/o Diabetes, smoking (in the past / present) family h/o IHD and they were clinically examined for hypertension ,body mass index for Obesity and features of RA. Pt with BP >140/90 mmhg were considered as hypertensives in this study. Fasting blood for sugar and lipid profile were measured. They were also evaluated for RF titres by ELISA. A resting 12 lead ECG was carried out for features of IHD. The following changes in the ECG were taken as marker of ischemia

1) The combination of ST elevation in a set of leads and reciprocal ST depression in a set of leads.
2) Inversion of T with ST still being elevated.
3) Presence of pathological Q waves

Statistical analysis:

Statistical analysis was done using standard formulae SPSS(Statistical Package for social sciences) in windows Dos version. Base line data like age, gender, RF, Traditional risk factors were collected. Patients were categorized on their RF positive with or without traditional risk factors and Ischemic changes.

The significance of Association between the factors was collected using PEARSON CHI-SQUARE TEST and YATES Corrected CHI-SQUARE TEST. $P<0.05$ was taken as significant.

CRITERIA CONSIDERED IN THE STUDY

S.NO	PARAMETERS	VALUES
1	Obesity	>23
2	Hypertension:	>140/90mmhg
3	Diabetes -Fasting blood suger	> 110
4	Abnormal Lipid profiles;	
	VLDL:	>100 mg/dl
	LDL:	>100mg/dl
	HDL:	<40mg/dl
	TGL:	>160mg/dl
5	Rheumatoid factor;	
	Low titre:	<320IU/ml
	High titre:	>320IU/ml

OBSERVATIONS AND RESULTS

1.	**TOTAL NUMBERS OF PATIENTS(n)**	:100
	FEMALE	:65
	MALE	:35
2.	**AGE**	
	<40YEARS	:43
	40-60YEARS	:57
3.	**ECG-ISCHEMIC CHANGES**	
	TOTAL	:16
	A. WITH TRADITIONAL FACTORS	:12
	MALE	:7
	FEMALE	:5
	B. ONLY RF POSITIVE	:4
	MALE	:4
	FEMALE	:0
	HIGH TITRE- RF	:3
	LOW TITRE-RF	:1

AGE DISTRIBUTION

Of the hundred patients with RF positivity , there were 65 females and 35 males, age distribution of those included in the study are showed in table no:1

TABLE NO-1 AGE DISTRIBUTION IN RELATION TO SEX

AGE	MALE	FEMALE
<20	0	2
20-30	5	12
30-40	7	17
40-50	20	30
50-60	3	4

CHART NO-1 AGE DISTRIBUTION IN RELATION TO SEX

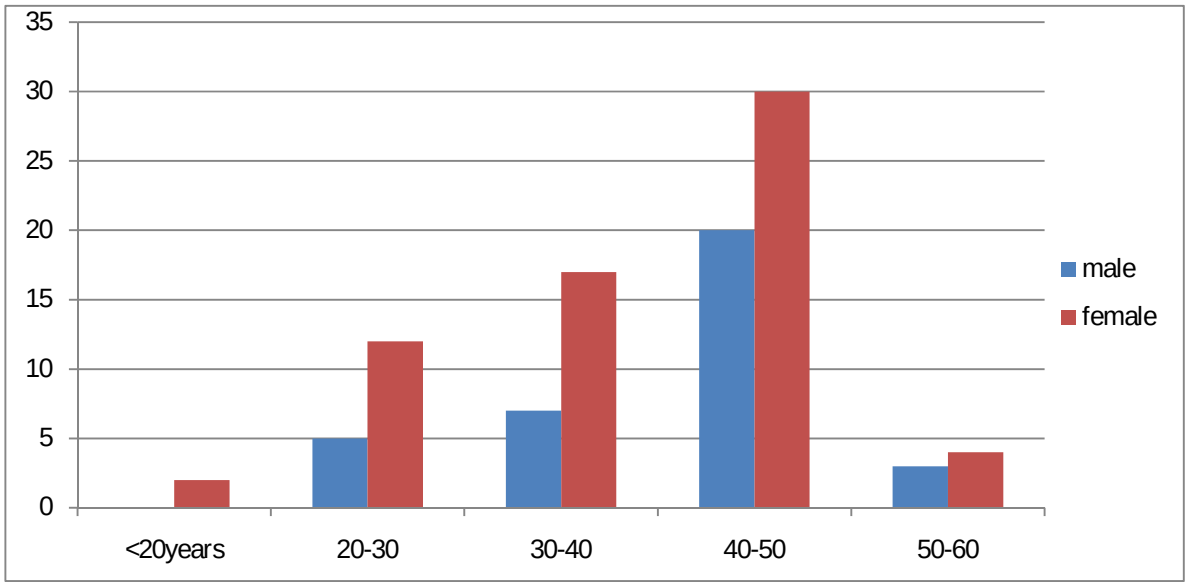


TABLE -2: ISCHEMIC CHANGES IN ECG IN RELATION TO PRESENCE OF RF AND TRADITIONAL RISK FACTORS

DISTRIBUTION OF PATIENTS SHOWING ISCHEMIC CHANGES ECG			
RF with traditional risk factor		**RF without Traditional risk factor**	
N=12 (75%)		N=4 (25%)	
M-7(43.75%)	F-5(31.25%)	M-4(25%)	F-0

CHART-2 : ISCHEMIC CHANGES IN RF POSITIVE PATIENTS

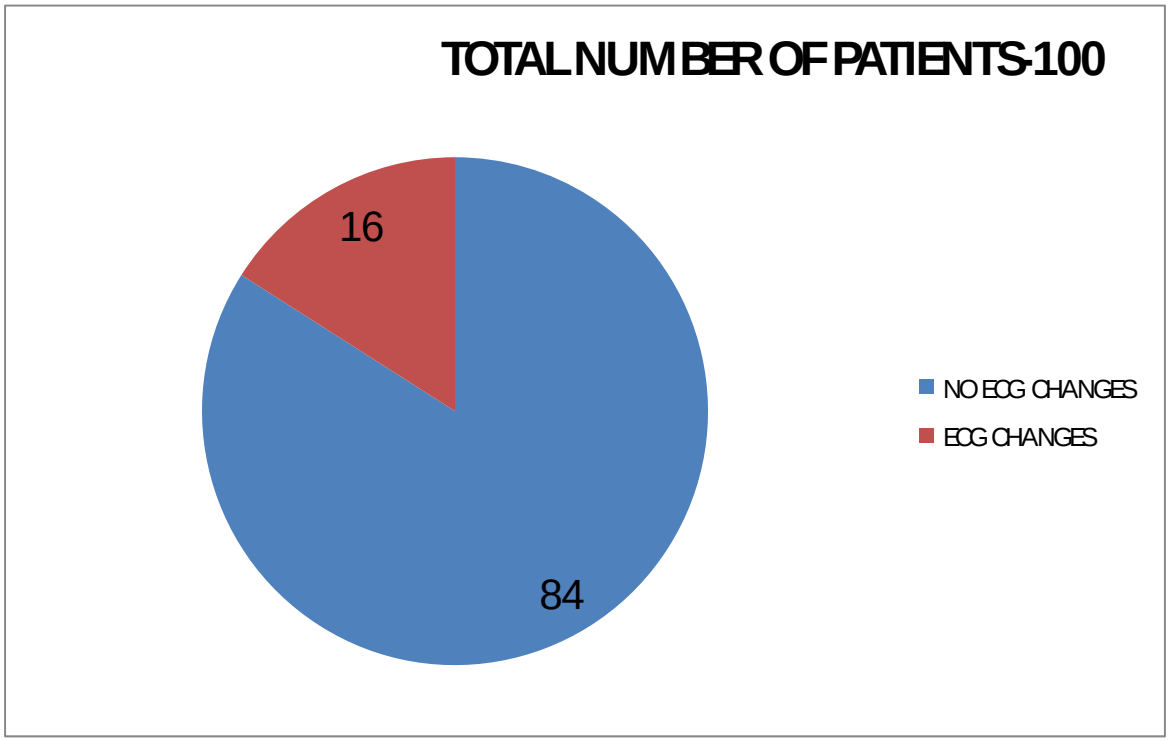
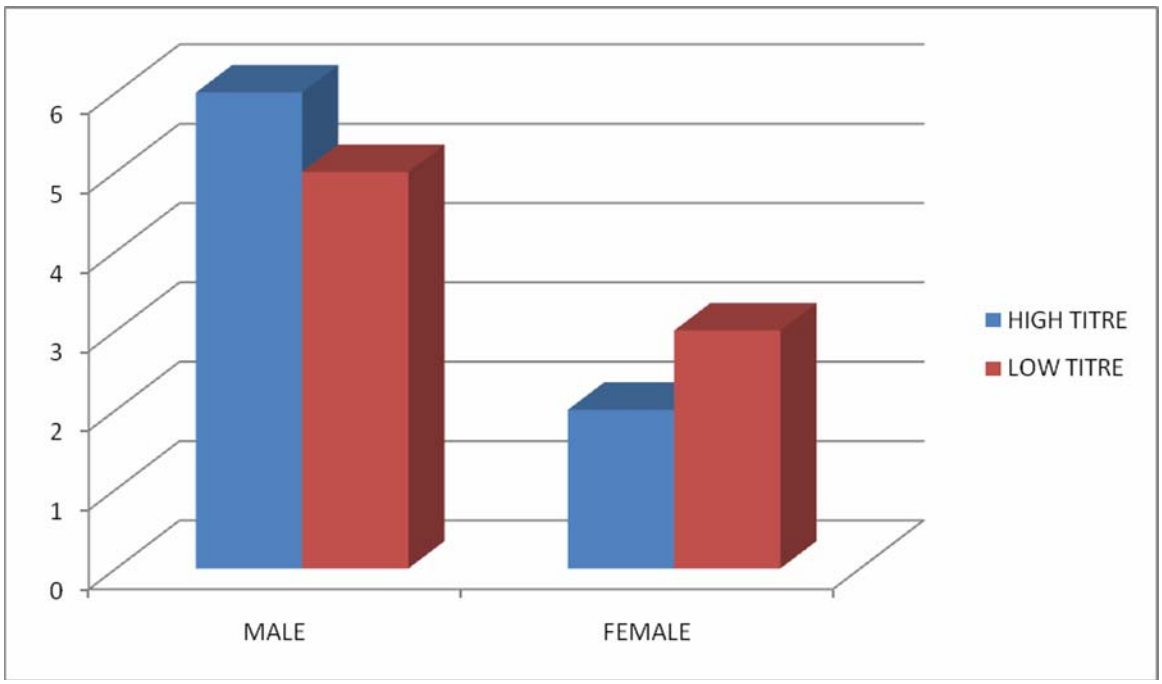


TABLE NO-3: SEX DISTRIBUTION OF ISCHEMIC CHANGES IN RELATION TO RF TITRES WITH TRADITIONAL RISK FACTORS

ISCHEMIC CHANGES IN ECG(N=16)			
MALE(11)		**FEMALE(5)**	
RF-HIGH TITRE	RF-LOW TITRE	RF-HIGH TITRE	RF-LOW TITRE
6 (37-5%)	5 (31.25%)	2 ((12.5%)	3 (18.75%)

CHART-3: ISCHEMIC CHANGES INRELATION TO RF TITRE WITH AND WITHOUT TRADITIONAL RISK FACTORS



In the present study there were 16 patients who had RF positivity with Ischemic changes in ECG.11 were males and 5 were females.Of these 6 males and 2 females had high titre of RF with ischemic changes.

Considering the association of traditional risk factors as an additional factor with RF positivity,12 had ischemic changes. There were 4 males who had only RF positivity without traditional risk factors.

TABLE -4: AGE AND SEX DISTRIBUTION IN RELATION TO ISCHEMIC CHANGES OF RF WITH TRADITIONAL RISK FACTORS

AGE DISTRIBUTION OF ISCHEMIC CHANGES		
AGE	**MALE**	**FEMALE**
<20	0	0
20-30	1 (6.25%)	0
30-40	4 (25%)	1 (6.25%)
40-50	4 (25%)	2 (18.75%)
50-60	2 (12.5%)	1 (6.25%)

TABLE -5: AGE DISTRIBUTION IN RELATION TO ISCHEMIC CHANGES OF RF WITH TRADITIONAL RISK FACTORS

ECG-ISCHEMIC CHANGES		
AGE	**NUMBERS**	**PERCETAGE**
40 yrs	6	37.5%
41-60yrs	10	62.5%

$\chi 2=1.19$

P=0.28 NOT SIGNIFICANT

On comparing below 40age : 40-60age 1:1.66 ratio by chi square test, the P value is 0.28 which is > 0.05.so,it is not significant. The association between age distribution in RF positive patients is not significant.

CHART -4: AGE DISTRIBUTION IN RELATION TO ISCHEMIC CHANGES OF RF WITH TRADITIONAL RISK FACTORS

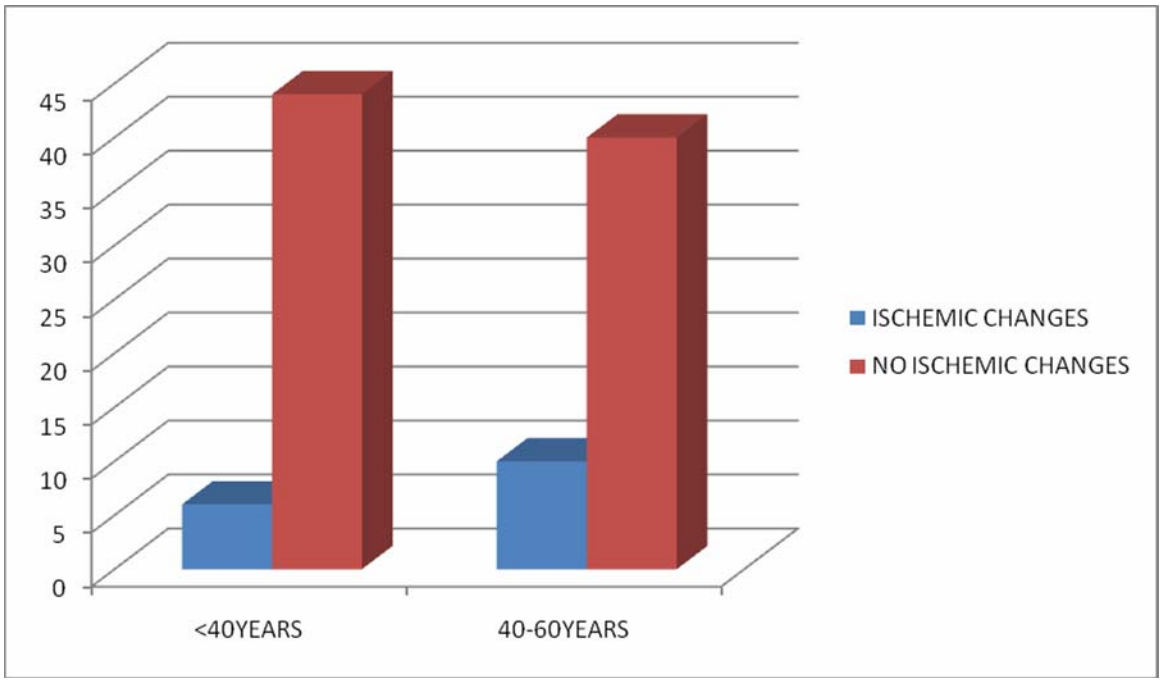


TABLE-6: SEX DISTRIBUTION IN RELATION TO ISCHEMIC CHANGES DUE TO RF WITH TRADITIONAL RISK FACTORS

ECG-ISCHEMIC CHANGES		
SEX	**NUMBERS**	**PERCENTAGE**
MALE	11 (35)	31.4%
FEMALE	5 (65)	7.7%

$\chi 2$= 9.53 / P=0.002 SIGNIFICANT

31.4% of male and 7.7% of females with RF positive with traditional risk factors had ischemic changes . On comparing the female, male ratio (2.2 :1) by chi square test, the P value is 0.002. This indicating that males with RF and traditional risk factors have greater risk of IHD compared to females.

CHART-5: SEX DISTRIBUTION IN RELATION TO ISCHEMIC CHANGES DUE TO RF WITH TRADITIONAL RISK FACTORS

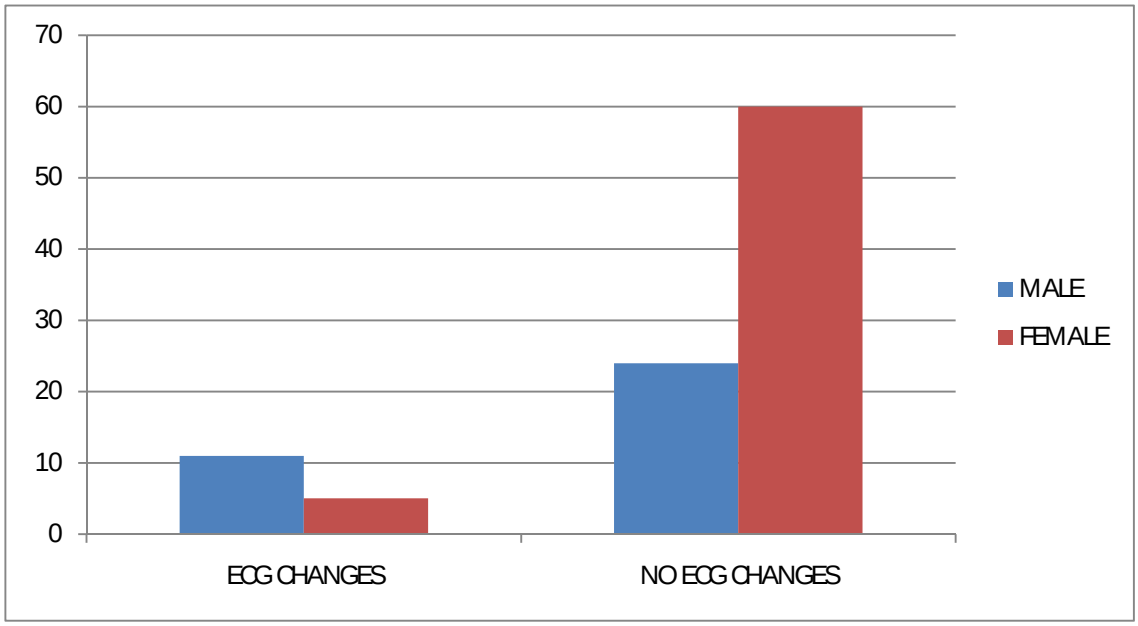


TABLE-7: SEX DISTRIBUTION OF ISCHEMIC CHANGES IN RELATION TO RF TITRES WITH TRADITIONAL RISK FACTORS

ISCHEMIC CHANGES IN ECG(N=16)			
MALE(11)		**FEMALE(5)**	
RF-HIGH TITRE	RF-LOW TITRE	RF-HIGH TITRE	RF-LOW TITRE
6 (37.5%)	5 (31.25%)	2 ((12.5%)	3 (18.75%)

CHART-6: SEX DISTRIBUTION OF ISCHEMIC CHANGES IN RELATION TO RF TITRES WITH TRADITIONAL RISK FACTORS

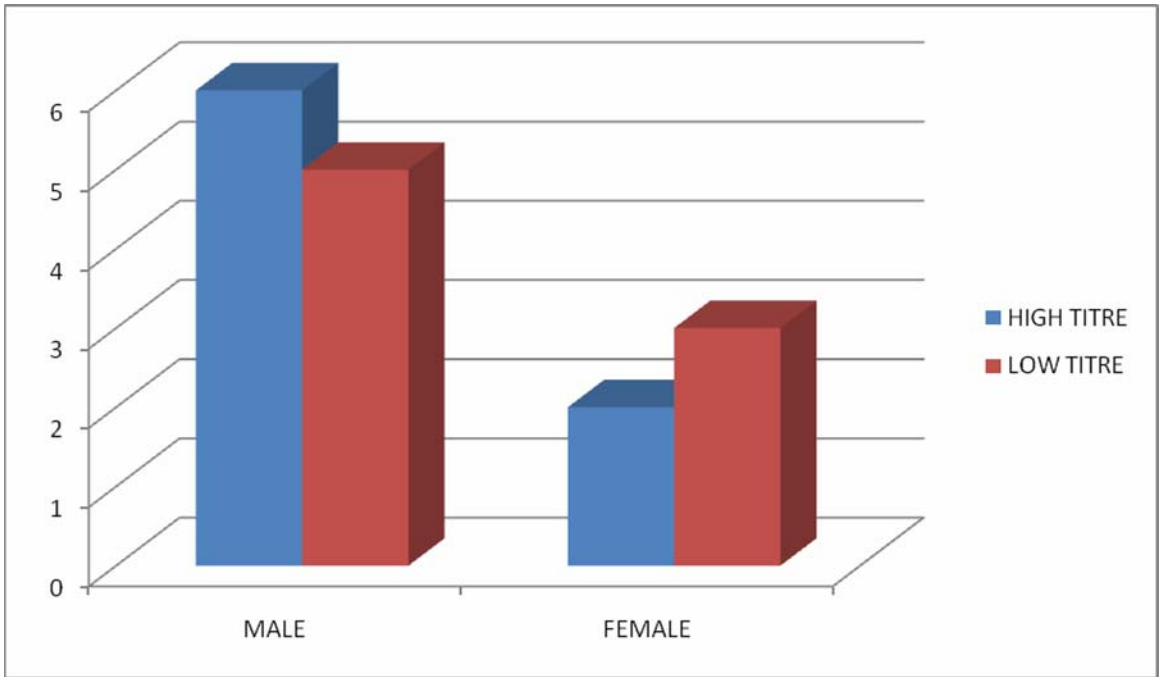


TABLE-8: ISCHEMIC CHANGES IN RELATION TO RF WITH AND WITHOUT TRADITIONAL RISK FACTORS IN PERCENTAGE.

ECG-ISCHEMIC CHANGES(N=16)		
TRADITIONAL RISK FACTORS	**NUMBERS**	**PERCENTAGE**
PRESENT	12	75%
NOT PRESENT	4	25%

$\chi 2$= 22.3 ; P=0.001 SIGNIFICANT

Of this ischemic changes in RF positive with traditional risk factors are 44.4 % without traditional risk factors are 5.5 % . On comparing these 3:1 ratio by chi square test , P value is 0.001which is statistically significant.

CHART-7: ISCHEMIC CHANGES IN RELATION TO RF WITH AND WITHOUT TRADITIONAL RISK FACTORS .

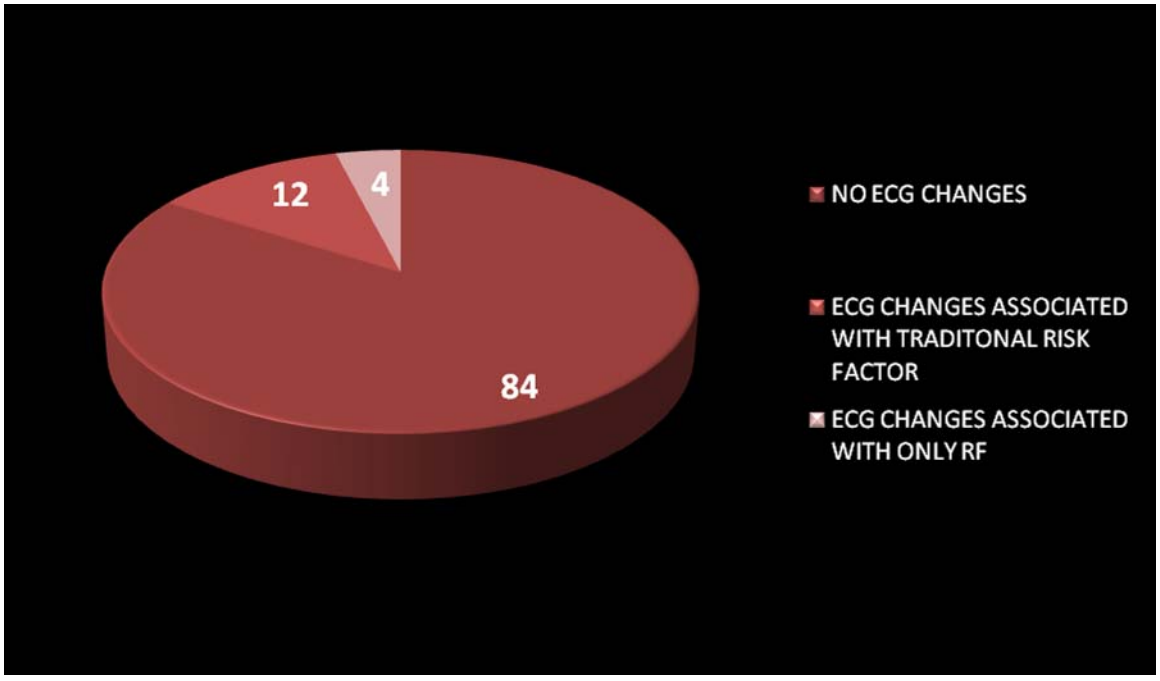
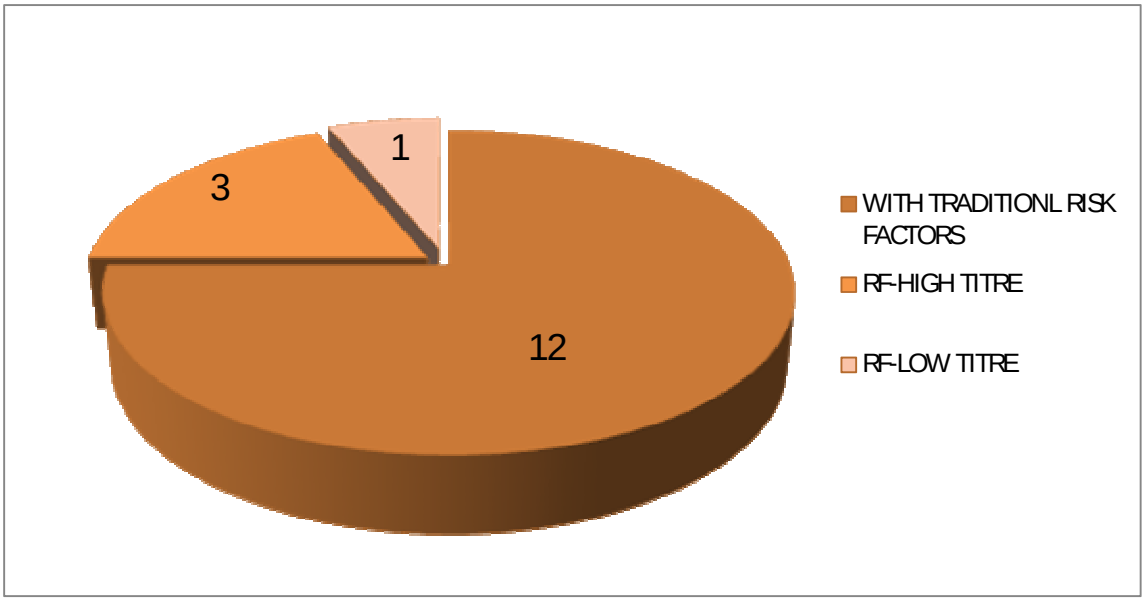


TABLE- 9: SEX DISTRIBUTION IN RELATION TO ISCHEMIC CHANGES IN LONE RF POSITIVE AND TITRES

ISCHEMIC CHANGES IN ECG(N=4)			
MALE(4)		**FEMALE(0)**	
RF-HIGH TITRE	RF-LOW TITRE	RF-HIGH TITRE	RF-LOW TITRE
3 (75%)	1 (25%)	0	0

CHART-8 : ISCHEMIC CHANGES IN ECG RELATION TO LONE RF POSITIVE AND TITRES



Lone RF without traditional risk factors was seen in only 4 male patients.there were no female patient .Of the 4 male patients 3 had high titre RF (>350).

In men

4/35 ==11.495%

CONFIDENCE INTERVEL= 4 – 28

χ^2**YATES CORRECTED** **P**=0.01 SIGNIFICANT

In study population

4/100== 4%

CONFIDENCE INTERVEL= is 1.7-5.4.

χ^2**YATES CORRECTED** **P**=0.01 SIGNIFICANT

DISCUSSION

In the study population, most of the RF positive patients clustered between 30-50 years. Dividing the study population with ischemic changes by ECG, by age, 6% were below 40 years and 10% were above 40 years. All of the above patients had RF positivity along with traditional risk factors and ischemic changes in the ECG.

In this study 35% were males and 65% were females. The M:F ratio was 1: 1.8. 16 patients had ischemic changes in ECG constituting 11males (31.1%) and 5 females (7.7%)patients. This is concordant with Edwards C J et al[1] where the M:F ratio was 1 : 1.02 . Comparatively females were more common in present study population. This is because the patients selected were suffering RA which is more common in females. Considering the ischemic changes, males were affected more than females though more number of female patients were included in the study. This is also similar to Edwards C J et al[1]

Evaluating the 16%(n=16) who were RF positive with Ischemic changes 12 patients had traditional risk factors(75%).The other 4 patients had only RF positivity without any other risk factor. All these 4 patients were males. This indicates an association of RF and IHD a strong possibility especially in males.

Among the 11male patients who had RF positivity with traditional risk factors and ischemic changes, 6 patients had high titre of RF and 5 patients had

low titre. Percentage wise 37.5% and 31.25% were having high and low titres of RF along with traditional risk factors causing IHD. This is concordant with both Edwards C J et al[1], Kenneth J Warrington et al[4.]

Among the 5female patients who had RF positivity with traditional risk factors , 2 patients had ischemic changes with high titre of RF making up 12.5%. 3 patients had ischemic changes with low titre RF and traditional risk factors forming 18.75% This is disconcordant with both Edwards C J et al[1], Kenneth J Warrington et al[4.]

By these data we can conclude, RF with traditional risk factor have increased incidence of ischemic changes in males than females especially high titre RF.

In this study only 4 patients had RF positivity without traditional risk factors along with ischemic changes and all of them were males.This is 36.3% of the total RF positive males in study population and 11.495% total male patients. No female patients had lone RF without traditional risk factor. This study is in concordance with Edwards C J et al[1]

The long term Herfordshire Cohort study reported by Sydall H E et al[5] had similar results. RF positive male patients without traditional risk factors are vulnerable to IHD. Females with traditional risk factors did not have IHD – this is discordant with this study. Our study indicated that IHD may be associated with

RF and traditional risk factors in females which is as in the study of Sydall H E et al[5]

Of these 4 male patients, 3 patients had high titre of RF positivity which is 75% and one patient had low titre of RF which is 25% .This suggested that a high titre of RF may have an increased incidence of IHD. This concurs with the earlier study by Edwards C J et al[1] and del Puente A et al[3]

In this study, Autoantibody RF which is risk factor for IHD in men is 11.495% (4 out of 35); confidence interval(CI) is 4-28 and 4% (4out of 100) study population; This goes with many other similar studies from various parts of the world.

Most of the of the studies state the prevalence to be between 4-28%. Edwards C J et al[1]- 11.6%(in men), Kenneth J Warrington1 et al[4] -1.97% (in general population).

From the observation and analysis of study assumed that there is an association between high titre of RF and IHD.This association was significantly more in male patients.

This study has a number of potential limitations. The most important is the fact that this is a cross-sectional study and will need confirmation by a longitudinal cohort study.

CONCLUSIONS

- RF per se can be considered as one of the risk factor for Ischemic heart disease in males.
- High titre RF alone can further increase the Incidence of IHD.
- RF associated with traditional risk factors increase the prevalence of IHD.
- Though more female patients have positive RF ,they are not vulnerable to IHD

BIBILOGRAPHY

1) Edwards C J; Syddall, H;Goswami,R;Goswmi,P;Dennison et al behalf of the Hertfortshire cohort study group 93(10)2007,1263-67
2) Nielen M M,vanschaardenberg D,Reesink H W,et al . Specific autoantibodies precede the symptoms of rheumatoid arthritis:a study of serial measurements in blood donors.Arthritis Rheum 2004;50:380-6.
3) Del Puente A,Knowler W C,Pettitt DJ, et al. The incidence of rheumatoid arthritis is predicted by rheumatatoid factor titer in a longitudinal population study.Arthritis Rheum 1988;31:1239-44.
4) Kenneth J Warrington, Peter D Kent, Robert L Frye, James F Lymp, Stephen L Kopecky;Jörg J Goronzy and Cornelia M Weyand
5) Syddall H E Aihie sayer A, Dennison E M,et al. Cohort profile:the Hertfordshire Cohort Study .Int J Epidimiol 2005;34:1234-42.
6) Khot U N, Khot M B, Bajzer C T,et al.prevalance of conventional risk factors in patients with coronary heart disease.JAMA 2003;290:898-904.
7) Ridker P M,Cushman M, Stampfer M J,et al. Inflammation,asprin, and the risk of cardiovascular disease in apparently healthy men.N Engl J Med 1997;336:973-9.

8) Wolfe F, Freundich B, StrussW L.Increase in cardiovascular and cerebrovascular disease prevalence in rheumatoid arthritis.J Rheumatol 003 ;30:36-40.

9) Mikkelsen W M, Dodge H J,Duff l f,et al. Estimates of the prevalence of rheumatic disease in the population of Tecumseh,Michigan,1959-60 J Chronic Dis 1967;20:351-69.

10) Goodson N J,Symmons D P,Scott D G et al.Baseline levels of C-reactive protein and prediction of death from cardiovascular disease in patients with inflammatory poly arthritis:Arthritis Rheum 2005;52:2293-9.

11) Ross R: Atherosclerosis – an inflammatory disease. *N Engl JMed* 1999, 340:115-126.

12) Weyand CM, Goronzy JJ, Liuzzo G, Kopecky SL, Holmes DR Jr,Frye RL: T-cell immunity in acute coronary syndromes. *Mayo Clini Proc* 2001, 76:1011-1020.

13) Ridker PM, Hennekens CH, Buring JE, Rifai N: C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med* 2000, 342:836-843.

14) Liuzzo G, Biasucci LM, Gallimore JR, Grillo RL, Rebuzzi AG, Pepys MB, Maseri A: The prognostic value of C-reactive protein and serum amyloid a protein in severe unstable angina. *N Engl J Med* 1994,331:417-

424.

15) Libby P: Coronary artery injury and the biology of atherosclerosis: inflammation, thrombosis, and stabilization. *Am J Cardiol*2000, 86:3J-8J. discussion 8J-9J

16) Liuzzo G, Kopecky SL, Frye RL, O'Fallon WM, Maseri A, GoronzyJJ,Weyand CM: Perturbation of the T-cell repertoire in patients with unstable angina. *Circulation* 1999, 100:2135-2139.

17) Liuzzo G, Vallejo AN, Kopecky SL, Frye RL, Holmes DR, Goronzy JJ, Weyand CM: Molecular fingerprint of interferon-gamma signaling in unstable angina. *Circulation* 2001, 103:1509-1514.

18) Warrington KJ, Takemura S, Goronzy JJ, Weyand CM: CD4+,CD28- T cells in rheumatoid arthritis patients combine features of the innate and adaptive immune systems. *Arthritis Rheum* 2001, 44:13-20.

19) Liuzzo G, Goronzy JJ, Yang H, Kopecky SL, Holmes DR, Frye RL,Weyand CM: Monoclonal T-cell proliferation and plaque instability in acute coronary syndromes. *Circulation* 2000, 101:2883-2888.

20) Nakajima T, Schulte S, Warrington KJ, Kopecky SL, Frye RL, Goronzy JJ, Weyand CM: T-cell-mediated lysis of endothelial cells in acute coronary syndromes. *Circulation* 2002,105:570-575.

21) Martens PB, Goronzy JJ, Schaid D, Weyand CM: Expansion of unusual CD4+ T cells in severe rheumatoid arthritis. *Arthritis Rheum* 1997, 40:1106-1114.

22) Harris EJ: *Rheumatoid Arthritis* Philadelphia: W.B. Saunders; 1997. Solomon DH, Karlson EW, Rimm EB, Cannuscio CC, Mandl LA,Manson JE, Stampfer MJ, Curhan GC: Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis.*Circulation* 2003,107:1303-1307.

23) Park YB, Ahn CW, Choi HK, Lee SH, In BH, Lee HC, Nam CM, Lee SK: Atherosclerosis in rheumatoid arthritis: morphologic evidence obtained by carotid ultrasound. *Arthritis Rheum* 2002,46:1714-1719.

24) Del Rincon I, Williams K, Stern MP, Freeman GL, O'Leary DH, Escalante A: Association between carotid atherosclerosis and markers of inflammation in rheumatoid arthritis patients and healthy subjects. *Arthritis Rheum* 2003, 48:1833-1840.

25) Prior P, Symmons DP, Scott DL, Brown R, Hawkins CF: Cause of death in rheumatoid arthritis. *Br J Rheumatol* 1984, 23:92-99.

26) Mutru O, Laakso M, Isomaki H, Koota K: Cardiovascular mortality in patients with rheumatoid arthritis. *Cardiology* 1989,76:71-77.

27) Wolfe F, Mitchell DM, Sibley JT, Fries JF, Bloch DA, Williams CA,

Spitz PW, Haga M, Kleinheksel SM, Cathey MA: The mortality of rheumatoid arthritis. *Arthritis Rheum* 1994, 37:481-494.

28) Myllykangas-Luosujarvi R, Aho K, Kautiainen H, Isomaki H: Cardiovascularmortality in women with rheumatoid arthritis. *J Rheumatol* 1995, 22:1065-1067

29) Wallberg-Jonsson S, Johansson H, Ohman ML, Rantapaa-Dahlqvist S: Extent of inflammation predicts cardiovascular disease and overall mortality in seropositive rheumatoid arthritis. A retrospective cohort study from disease onset. *J Rheumatol* 1999,26:2562-2571.

30) Jacobsson LT, Turesson C, Hanson RL, Pillemer S, Sievers ML, Pettitt DJ, Bennett PH, Knowler WC: Joint swelling as a predictor of death from cardiovascular disease in a population study of Pima Indians. *Arthritis Rheum* 2001, 44:1170-1176.

31) Burggraf GW, Parker JO: Prognosis in coronary artery disease.Angiographic, hemodynamic, and clinical factors. *Circulation*1975, 51:146-156.

32) Kumeda Y, Inaba M, Goto H, Nagata M, Henmi Y, Furumitsu Y, Ishimura E, Inui K, Yutani Y, Miki T, *et al.*: Increased thickness of the arterial intima-media detected by ultrasonography in patients with rheumatoid arthritis. *Arthritis Rheum* 2002,46:1489-1497.

33) McEntegart A, Capell HA, Creran D, Rumley A, Woodward M, Lowe GD: Cardiovascular risk factors, including thrombotic variables, in a population with rheumatoid arthritis. *Rheumatology (Oxford)* 2001, 40:640-644.

34) del Rincon ID, Williams K, Stern MP, Freeman GL, Escalante A: High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors.*Arthritis Rheum* 2001, 44:2737-2745

35) Vaudo G, Marchesi S, Gerli R, Allegrucci R, Giordano A, Siepi D, Pirro M, Shoenfeld Y, Schillaci G, Mannarino E: Endothelial dysfunction in young patients with rheumatoid arthritis and low disease activity. *Ann Rheum Dis* 2004, 63:31-35.

36) Hurlimann D, Forster A, Noll G, Enseleit F, Chenevard R, Distler O, Bechir M, Spieker LE, Neidhart M, Michel BA, *et al.*: Anti-tumor necrosis factor-alpha treatment improves endothelial function in patients with rheumatoid arthritis. *Circulation* 2002,106:2184-2187

37) Asherson RA and Cervera R. The Antiphospho-lipid Syndrome. In: Textbook of the Autoimmune diseases. (eds. RG Lahita, N Chirozzi and WH Reeves). Lippinkot Williams & Wilkins, Philadelphia, 2000, pp. 641-668.

38) Adler Y, Finkelstein Y, Zandeman-Goddard G et al. The presence of

antiphospholipid antibodies in acute myocardial infarction. Lupus 1995, 4:309-13.

39) Badui E, Solorio S, Martinez E et al. The heart in the primary antiphospholipid syndrome. Arch Med Res 1995, 26:115-120. Baker WF and Bick RL. Antiphospholipid antibodies in coronary artery disease:a review. Semin Thromb Hemost 1994, 20:27-45.

40) Seijas M, Martinez-Vazquez C, Rivera A, et al. Prevalence of antiphospholipid syndrome in patients under 65 years of age with acute myocardial infarction. Rev Clin Med 2001, 201:118-121

41) Vaarala O, Mänttäri M, Manninen V, et al. Anticardiolipin antibodies and risk of myocardial infarction in a prospective cohort of middle aged men. Circulation, 1995, 91:23-27.

42) Goodson NJ, Wiles NJ, Lunt M, Barrett E, Silman AJ, Symmons DPM. Mortality in early inflammatory polyarthritis: cardiovascular mortality is increased in seropositive patients. Arthritis Rheum 2002;46:2010-9.

43) Bazzano LA, He J, Muntner P, Vupputuri S, Whelton PK. Relationship between cigarette smoking and novel risk factors for cardiovascular disease in the United States. Ann Intern Med 2003;138:891-7.

44) Turesson C, McClelland RL, Christianson TJ, Matteson EL. Severe extra-articular disease manifestations are associated with an increased risk of first ever cardiovascular events in patients with rheumatoid arthritis. Ann Rheum Dis 2007;66:70-5.

45) Gonzalez A, Maradit Kremers H, Crowson CS, et al. Do cardiovascular risk factors confer the same risk for cardiovascular outcomes in rheumatoid arthritis patients as in non-rheumatoid arthritis patients? Ann Rheum Dis 2008;67:64-9.

46) Wallberg-Jonsson S, Ohman M, Rantapaa-Dahlqvist S. Which factors are related to the presence of atherosclerosis in rheumatoid arthritis? Scand J Rheumatol 2004;33:373-9.

47) Roman MJ, Moeller E, Davis A, et al. Preclinical carotid atherosclerosis in patients with rheumatoid arthritis. Ann Intern Med 2006;144:249-56.

48) Jacobsson LT, Turesson C, Hanson RL, et al. Joint swelling as a predictor of death from cardiovascular disease in a population study of Pima Indians. Arthritis Rheum 2001;44:1170-6.

49) Maradit-Kremers H, Nicola PJ, Crowson CS, Ballman KV, Gabriel SE. Cardiovascular death in rheumatoid arthritis: a population-based study. Arthritis Rheum 2005;52:722-32.

50) Goodson NJ, Symmons DPM, Scott DGI, Bunn D, Lunt M, Silman AJ. Baseline C-reactive protein and prediction of death from cardiovascular disease in patients with inflammatory polyarthritis. Arthritis Rheum 2005;52:2293-9.

51) Saag KG, Cerhan JR, Kolluri S, Ohashi K, Hunninghake GW, Schwartz DA. Cigarette smoking and rheumatoid disease severity. Ann Rheum Dis 1997;56:463-70.

52) Farragher TM, Lunt M, Bunn DK, Silman AJ, Symmons DP. Early functional disability predicts both all-cause and cardiovascular mortality in people with inflammatory polyarthritis: results from the Norfolk Arthritis Register. Ann Rheum Dis 2007;66:486-92.

53) Wolfe F, Michaud K, Gefeller O, Choi HK. Predicting mortality in patients with rheumatoid arthritis. Arthritis Rheum 2003; 48:1530-42.

54) Tracy RP. Inflammation markers and coronary heart disease. Curr Opin Lipidol 1999;10:435-41.

55) Ridker PM. Connecting the role of C-reactive protein and statins in cardiovascular disease. Clin Cardiol 2003;26:1139-44.

56) Jensen G and Sigurd B: Systemic lupus erythematosus and acute myocardial infarction. Chest 64: 653, 1973.

57) Rosenthal T, Neufeld H, Kishon Y, et al: Myocardial infarction in a young womanwith SLE. Angiology 31:573, 1980.

58) Tsakralides VG, Blieden LC, Edwards JE, et al: Coronary atherosclerosis and myocardial infarction associated with systemic lupus erythematosus. Am Heart J 87: 637, 1974.

59) Spiera H, Rothenberg RR: Myocardial infarction in four young patients with SLE. J Rheumatol 10: 464, 1983.

PROFORMA

Name:

Age:

Sex:

OP No.

Address:

Presenting Complaints:-

H/o HT

H/o Diabetes Mellitus

H/o IHD

H/o Smoking

Family H/o IHD

Rhematalogical H/O

EXAMINATION:

Pulse:

BP:

CVS:

RS:

P/A:

CNS:

INVESTIGATIONS:

BLOOD GLUCOSE:

Fasting

Post prandial

S.LIPID PROFILE:

TOTAL CHOLESTROL

VLDL

LDL

HDL

TGL

BODY MASS INDEX :

RHEUMATOID FACTOR:

High titre

Low titre

ELECTROCARDIOGRAM:

ECHO :

INSTITUTIONAL ETHICAL COMMITTEE
GOVERNMENT GENERAL HOSPITAL & MADRAS MEDICAL COLLEGE,
CHENNAI-600 003.

Telephone: 044-2530 5000

Fax : 044 – 25305115

K.Dis.No.16328 P & D3/Ethies/Dean/GGH/08 Dated: 8/9/2008

Title of the work : **A STUDY OF RHEUMATOID FACTOR AND ITS RELATION TO ISCHEMIC HEART DISEASE**

Principal Investigator : **DR .P.JAYAPANDIAN**

Department : **INSTITUTE OF INTERNAL MEDICINE, MMC, CHENNAI 3**

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 10th sep 2008 at 2 P.M in GI GH , Deans, Chamber, Chennai-3.

The members of the Committee, the Secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The principal investigator and their term are directed to adhere the guidelines given below:

1. You should get detailed informed consent from the patients/participants and maintain confidentiality.
2. You should carry out the work without detrimental to regular activities as well as without extra expenditure to the Institution or Government.
3. You should inform the IEC in case of any change of study procedure, site and investigation or guide.
4. You should not deviate form the area of the work for which I applied for ethical clearance.
5. You should inform the IEC immediately, in case of any adverse events or serious adverse reactions.
6. You should abide to the rules and regulations of the institution(s)
7. You should complete the work within the specific period and if any extension of time is required, you should apply for permission again and do the work.
8. You should submit the summary of the work to the ethical committee on completion of the work.
9. You should not claim funds from the Institution while doing the work or on completion.
10. You should understand that the members of IEC have the right to monitor the work with prior intimation.

SECRETARY
IEC, GGH,CHENNAI

CHAIRMAN
IEC, GGH,CHENNAI

DEAN
GGH &MMC, CHENNAI

RKM.5.6(2)

MASTER CHART

S.no	Name	Age	Sex	Rheumatoid arthritis	Traditional risk factor	Rheumatoid factor	Ecg-ischemic Changes	Echo abnormality
1	SELVI	25	F	YES	NO	LT	NO	NO
2	RUKUMANI43	43	F	YES	NO	LT	NO	NO
3	SARASWATHY	46	F	YES	NO	HT	NO	NO
4	JEYASEELI	32	F	YES	YES	LT	NO	NO
5	THANGASAMY	48	M	YES	NO	LT	NO	NO
6	THARA	45	F	YES	NO	LT	NO	NO
7	ELCY SELVAKUMAR	28	F	YES	NO	HT	NO	NO
8	MUNUSAMY	51	M	YES	YES	HT	YES	YES
9	ZARINA	19	F	YES	NO	LT	NO	NO
10	VELMURUGAN	35	M	YES	NO	LT	NO	NO
11	PAULRAJ	45	M	YES	NO	LT	YES	YES
12	PUNITHA	36	F	YES	NO	HT	NO	NO
13	SANCHAMMAL	45	F	YES	NO	LT	NO	NO
14	MURUGAMMA	42	F	YES	NO	LT	NO	NO
15	GANESH	43	M	YES	YES	LT	NO	NO
16	SANTRA	33	F	YES	NO	HT	NO	NO
17	KRISNAVENI	50	F	YES	YES	LT	YES	NO
18	KANCHANA	28	F	YES	NO	HT	NO	NO
19	GURUPRAKASH	48	M	YES	NO	LT	NO	NO
20	RAJESWARI	32	F	YES	NO	LT	NO	NO

S.no	Name	Age	Sex	Rheumatoid arthritis	Traditional risk factor	Rheumatoid factor	Ecg-ischemic Changes	Echo abnormality
21	SEKAR	46	M	YES	YES	LT	NO	NO
22	ANJALAI	28	F	YES	NO	LT	NO	NO
23	GURUNATHAN	38	M	YES	NO	HT	YES	YES
24	PRIYA	19	F	YES	NO	LT	NO	NO
25	MOHANA	27	F	YES	NO	LT	NO	NO
26	SARATHA	50	F	YES	NO	LT	NO	NO
27	VASANTHA	45	F	YES	NO	HT	NO	NO
28	DHANABALAN	41	M	YES	NO	LT	NO	NO
29	VANITHA	50	F	YES	YES	LT	YES	YES
30	VEDHAM	45	M	YES	NO	LT	NO	NO
31	DHAMODHARAN	50	M	YES	NO	LT	NO	NO
32	VIMALA	40	F	YES	YES	HT	YES	YES
33	KRISNAMOORTHY	21	M	YES	NO	LT	NO	NO
34	SELVAKUMAR	40	M	YES	YES	HT	NO	NO
35	SABANBEGAM	25	F	YES	NO	LT	NO	NO
36	SUNDARI	40	F	YES	YES	LT	YES	YES
37	KUPPUSAMY	43	M	YES	NO	LT	NO	NO
38	GANESHARANI	39	F	YES	NO	LT	NO	NO
39	SHAJITHABEGAM	45	F	YES	NO	LT	NO	NO
40	PREMA	50	F	YES	NO	HT	NO	NO
41	PANCHATCHARAM	48	M	YES	NO	LT	NO	NO

S.no	Name	Age	Sex	Rheumatoid arthritis	Traditional risk factor	Rheumatoid factor	Ecg-ischemic Changes	Echo abnormality
42	BASKAR	46	M	YES	YES	LT	YES	YES
43	RAHGMATHNISHA	40	F	YES	NO	HT	NO	NO
44	RAJENDRAN	45	M	YES	YES	LT	NO	NO
45	RAJASEKAR	48	M	YES	NO	HT	YES	YES
46	BHUVANESWARI	40	F	YES	YES	LT	NO	NO
47	INDRA	42	F	YES	NO	HT	NO	NO
48	MEENA	40	F	YES	NO	LT	NO	NO
49	KUMARAPPAN	42	M	YES	YES	LT	YES	YES
50	THENMOZHI	36	F	YES	NO	HT	NO	NO
51	LAKSMI	33	F	YES	NO	HT	NO	NO
52	VARADHARAN	52	M	YES	YES	LT	NO	NO
53	SARASU	41	F	YES	NO	LT	NO	NO
54	HARIHARAN	41	M	YES	NO	LT	NO	NO
55	SHUNMUGAM	32	M	YES	NO	HT	YES	YES
56	RAMANAN	32	M	YES	NO	LT	NO	NO
57	AMIRTHARAJ	39	M	YES	YES	LT	NO	NO
58	SEETHA	43	F	YES	NO	LT	NO	NO
59	GRACEMARY	26	F	YES	NO	LT	NO	NO
60	ANURADHA	35	F	YES	NO	HT	NO	NO
61	JAYANTHY	30	F	YES	NO	LT	NO	NO
62	RANI	32	F	YES	NO	LT	NO	NO

S.no	Name	Age	Sex	Rheumatoid arthritis	Traditional risk factor	Rheumatoid factor	Ecg-ischemic Changes	Echo abnormality
63	ARULSELVAN	23	M	YES	NO	LT	NO	NO
64	MOHAMMED IBRAH	38	M	YES	YES	LT	YES	YES
65	MEENATCHI	34	F	YES	NO	LT	NO	NO
66	SALIMABEE	45	F	YES	NO	HT	NO	NO
67	VEDHAVATHI	25	M	YES	NO	LT	NO	NO
68	GOWRI	44	F	YES	NO	HT	NO	NO
69	KRISHNAN	50	M	YES	YES	LT	NO	NO
70	KOMALAM	28	F	YES	NO	LT	NO	NO
71	NAGABHOOSNAM	48	F	YES	NO	LT	NO	NO
72	SAROJA	45	F	YES	YES	HT	YES	YES
73	SHAMSATHBEGAM	35	F	YES	NO	LT	NO	NO
74	KOKILA	37	F	YES	NO	LT	NO	NO
75	PITCAIMUTHU	51	M	YES	YES	LT	YES	YES
76	PRAKASAM	42	M	YES	YES	LT	NO	NO
77	MANGARYARKARASI	45	F	YES	NO	LT	NO	NO
78	KAMATCHI	40	F	YES	NO	LT	NO	NO
79	GANDHI	47	M	YES	YES	LT	NO	NO
80	VASANTHA	50	F	YES	NO	HT	NO	NO
81	AMBIKA	40	F	YES	NO	LT	NO	NO
82	GOWSALYA	50	F	YES	YES	LT	NO	NO
83	MAHESWARI	43	F	YES	NO	LT	NO	NO

S.no	Name	Age	Sex	Rheumatoid arthritis	Traditional risk factor	Rheumatoid factor	Ecg-ischemic Changes	Echo abnormality
84	SHEELA	30	F	YES	YES	LT	NO	NO
85	JOTHY	40	M	YES	YES	HT	YES	YES
86	KARUPPAIAH	48	M	YES	YES	LT	NO	NO
87	KANNIYAMMAL	52	F	YES	NO	LT	NO	NO
88	REGINAMARY	25	F	YES	NO	HT	NO	NO
89	SHANTHY	45	F	YES	YES	LT	NO	NO
90	MALARVIZHI	40	F	YES	NO	LT	NO	NO
91	LAKSMIGEVI	29	F	YES	NO	HT	NO	NO
92	MALARKODI	33	F	YES	NO	LT	NO	NO
93	MALA	30	F	YES	NO	LT	NO	NO
94	NARASHIMMAN	47	M	YES	YES	HT	YES	YES
95	KANCHANA	24	F	YES	NO	LT	NO	NO
96	ANJAMMAL	46	F	YES	NO	LT	NO	NO
97	MURUGAMMA	39	F	YES	NO	LT	NO	NO
98	KUMAR	27	M	YES	NO	LT	NO	NO
99	MARIMMAL	48	F	YES	NO	LT	NO	NO
100	MOHANAVALLI	43	F	YES	NO	LT	NO	NO

ABBREVIATIONS

ACL : ANTI CARDIOLIPIN ANTIBODIES

AMI : ACUTE MYOCARDIAL INFARCTION

APS : ANTI PHOSPHOLIPID SYNDROME

BMI : BODY MASS INDEX

CCP : CITRULINATED CYCLIC POLYPEPTIDE

CHD : CORONARY HEART DISEASE

CRP : C-REACTIVE PROTEIN

CVD : CARDIO VASCULAR DISEASE

ESR : ERTHROCYTE SEDIMENTATION RATE

HDL : HIGH DENSITY LIPOPROTEIN

IHD : ISCHEMIC HEART DISEASE

LDL : LOW DENSITY LIPOPROTEIN

RA : RHEUMATOID ARTHRITIS

RF : RHEUMATOID FACTOR

SLE : SYSTEMIC LUPUS ERTHYMATOSUS

TGL : TRIGLYCERIDE

VLDL : VERY LOW DENSITY LIPOPROTEIN